Amendment #1
to RFP-NIH-NIAID-DMID-03-32

"Antibody Production Facility"

Amendment to Solicitation No.:	NIH-NIAID-DMID-03-32
Amendment No.:	1
Amendment Date:	October 16, 2002
RFP Issue Date:	September 20, 2002
Issued By:	Contracting Officer NIH/NIAID Contract Management Branch 6700-B Rockledge Drive Room 2230, MSC 7612 Bethesda, Maryland 20892-7612
Point of Contact:	Elizabeth Osinski, Contract Specialist
Name and Address of Offeror:	To All Offerors

The above numbered solicitation is amended as set forth below:

Below are questions and answers concerning this RFP.

Question 1 Are we expected to have identified collaborators for animal models? Would it be sufficient to state that protection models will be addressed through existing Contractor/NIAID collaborations or through NIAID investigators who will provide the products for further development through this contract? Are specific details required?

Animal protection assays are included in the Statement of Work. Offerors should propose a technical approach to conducting efficacy studies in small animal models. These services may be provided by the contractor or its subcontractor. Animal protection assays should be included in the cost estimate for Tasks 1, 2 and 3. For the purposes of the cost estimate, the Offeror can assume the following scenario: a fully human monoclonal antibody specific for botulinum serotype A toxin has been transferred to the facility for development and production. Your facility clones the relevant genes into your production vector/cell line. Efficacy of the antibodies produced in the new vector/cell line needs to be confirmed before advancing to production of material for Phase I.

Question 2 What would be provided for a starting point?

For Task 2, assume murine hybridomas as a starting point.

Question 3 Are offerors expected to give a time and cost proposal for each task and task modification (i.e. time and cost report for task 1 AND 1a, 1b, 1c, 1d)?

Yes.

Question 4 What does fully human mAbs mean (task 1)? Does that mean that a cell line producing a fully human (from a genetically modified mouse producing completely human constant and variable region) or a humanized antibody would be received for optimization, characterization, and scale-up?

Fully human antibodies refer to a cell line (or equivalent) that produces fully human antibodies.

Question 5 Is it necessary to include production of scFvs in the proposal?

Production of scFvs is part of the Statement of Work. Offerors should provide a technical approach for the production of scFvs. These, however, are not part of the cost estimate.

Question 6 The term validation (i.e. assays, purification SOPs, etc.) is used a number of times in the RFP. The graded nature of biologics with regard to FDA compliance enables analytical assays supporting Phase 1 and 2 trials to be "qualified," not validated, at this development stage. Both assays and processes are then "validated" during Phase 3/Commercial manufacture. Is the RFP expecting true validation for both assays and processes?

The offeror should provide current SOPs for all processes and assays that are called for to undertake the Statement of Work. A validation plan for both assays and process with timelines (including justifications for the timeline) as part of the submission should also be provided. Assays and Process should be moving from "qualified" to "validated" to support product evaluation prior to production for phase 2 clinical evaluation. For those assays being submitted, information on the specificity, sensitivity (including limits of quantitation and detection) should be provided. The response should also include information about the quality and source of reagents and controls as well.

Assays related to the evaluation of antibody potency will be specific for particular toxins. Offerors should propose qualified assays moving to validated assays under the scenario outlined in the revised Note to Offerors #2 for budget proposal purposes.

Question 7 What is the exact role of the sponsor/contract awardee in clinical studies anticipated in this RFP?

Please see Note #1 in the Notes to Offerors section of this RFP.

The following sections of this RFP are amended as set forth below:

-Page 9, Notes to Offerors, Note 1 is amended to read as follows:

Note 1: For proposal preparation and for purposes of preparing the cost estimate assume that Phase I/II trials would involve up to 200 healthy adult volunteers and require approximately 5 grams of purified antibody product in studies designed to determine safety and pharmacokinetic profiles of the antibodies. (The actual amounts required for these studies will be determined by the Project Officer and will depend on the estimated effective dose (mg/kg) of each product.) Products produced under this contract must be suitable for human clinical trials conducted under IND. Clinical trials will, most likely, be conducted in NIAID supported clinical facilities under IND's held by the NIAID. The cost of conducting such trial will NOT be incurred under this resultant contract for the Antibody Production Facility and should not be included in offeror's cost proposal.

In addition assume that::

a) for Task 1 a fully human monoclonal antibody specific for botulinum serotype A toxin has been transferred to the facility for development and production. Your facility clones the relevant genes into your production vector/cell line. Efficacy of the antibodies produced in the new vector/cell line needs to be confirmed both in vitro and in vivo before advancing to production of material for Phase I.

b) for Task 2 a murine hybridoma specific for botulinum serotype A toxin has been transferred to the facility for conversion to a chimeric antibody and production of chimeric material for Phase I. Efficacy of the chimeric antibody needs to be confirmed both in vitro and in vivo before advancing to production of material for Phase I.

c) for Task 3 a fully human monoclonal antibody specific for botulinum serotype A toxin has been transferred to the facility for development and production. Your facility clones the relevant genes into your production vector/cell line. Efficacy of the antibodies produced in the new vector/cell line needs to be confirmed both in vitro and in vivo before advancing to production of material for Phase I. Refer to Note #7 in the RFP for shipping responsibilities for the National Stockpile.

-On page 11 of the RFP under **INSTRUCTIONS FOR SUBMISSION OF TASK ORDERS,** the last paragraph is revised to read as follows:

ONLY ONE BUSINESS PROPOSAL SHALL BE SUBMITTED BY OFFERORS IN RESPONSE TO THIS RFP. The individual cost proposals for the tasks and modifications to the tasks as listed on the chart on the next page should be a part of this business proposal. The individual cost proposals are separate documents within the business proposal and may only consist of a few pages each. The individual cost proposals shall be clearly labeled with titles such as *Task 1 Modification-3 fully human antibodies*, etc. For purposes of preparing these cost proposals, offerors should assume the following scenario will take place:

SCENARIO for preparing cost proposals: SEE NOTE TO OFFERORS #1.

-Add the following to the bottom of the chart of page 12 of this RFP. For all cost proposals for the tasks and task modifications to be submitted under this RFP, use Botulinum serotype A toxin for cost proposal preparation purposes. Refer to the revised **Note #1** to offeror above for additional information.

-On Page 13, Task Order #1, Paragraph B, Task Description is revised to read as follows:

B. Task Description – Task #1

The Contractor shall produce 1 fully human Ab in accordance with items 1 through 12 of the Statement of Work. ***For the purposes of preparing this cost proposal, offerors should use Botulinum Serotype A Toxin.*** For the purpose of this task order cost and time proposal **only** the offeror should assume that this task will be for the production of one fully human mAb sufficient to evaluate safety and pharmacokinetic profiles in 200 healthy adult volunteers and require approximately 5 grams of purified antibody product. (The actual amounts required for these studies will be determined by the Project Officer and will depend on the estimated effective dose (mg/kg) of each product.) Products produced under this contract must be suitable for human clinical trials conducted under IND. Clinical trials will, most likely, be conducted in NIAID supported clinical facilities under IND's held by the NIAID. The cost of conducting such trial will NOT be incurred by the APF and should not be included in offeror's cost proposal.

In addition assume that a fully human monoclonal antibody specific for botulinum serotype A toxin has been transferred to the facility for development and production. Your facility clones the relevant genes into your production vector/cell line. Efficacy of the antibodies produced in the new vector/cell line needs to be confirmed both in vitro and in vivo before advancing to production of material for Phase I.

At the time of contract award, the offeror will be directed by the Project Officer as to which products will be required in the first year of the Award.

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-On page 14, Task Order #2, Paragraph B, Task Description is revised as follows:

B. Task Description – Task #2

The Contractor shall produce 1 murine chimeric monoclonal antibody per year, including its conversion from a murine mAb in accordance with items 1 through 12 of the Statement of Work. For the purpose of this task order cost and time proposal **only,** the offeror should assume that this task will be for the conversion of **one** murine mAb to a chimeric mAb. ***For the purposes of preparing this cost proposal, offerors should use Botulinum Serotype A Toxin.*** For the purpose of this task order cost and time proposal **only** the offeror should assume that this task will be for the production of one human/murine chimeric mAb sufficient to evaluate safety and pharmacokinetic profiles in 200 healthy adult volunteers and require approximately 5 grams of purified antibody product. (The actual amounts required for these studies will be determined by the Project Officer and will depend on the estimated effective dose (mg/kg) of each product.) Products produced under this contract must be suitable for human clinical trials conducted under IND. Clinical trials will, most likely, be conducted in NIAID supported clinical facilities under IND's held by the NIAID. The cost of conducting such trial will NOT be incurred by the APF and should not be included in offeror's cost proposal.

In addition assume that a murine hybridoma for a monoclonal antibody specific for botulinum serotype A toxin has been transferred to the facility for development and production. Efficacy of the new chimeric

antibodies needs to be confirmed both in vitro and in vivo before advancing to production of material for Phase I.

At the time of contract award, the offeror will be directed by the Project Officer as to which products will be required in the first year of the Award.

On page 17, Task Order #3, Paragraph B, is revised to read as follows:

B. Task Description #3

The Contractor shall be required to produce large quantities of therapeutic Abs that show good safety and activity profiles in Phase I/II clinical trials for the National Pharmaceutical Stockpile. The Contractor shall . produce 1 fully human Ab in accordance with items 1 through 12 of the Statement of Work. For the purpose of this task order cost and time proposal **only,** the offeror should assume that this task will be for the production of one fully human mAb sufficient to for 100,000 doses or approximately 1 kilogram of purified antibody product. The should include storing, vialing, labeling, tracking and packaging in their cost and time estimate for this Task. The Contractor will not be required to ship products to the National Stockpile. ***For the purposes of preparing this cost proposal, offerors should use Botulinum Serotype A Toxin***. At the time of contract award, the offeror will be directed by the Project Officer as to which products will be required in the first year of the Award.

Except as provided herein, all terms and conditions of the RFP document NIH-NIAID-DMID-03-32 remain unchanged and in full force and effect.

The hour and date specified for receipt of offers is **NOT** extended.

Offerors must acknowledge receipt of this Amendment #1, by the following method:

- By acknowledging receipt of the amendment on each copy of the offer submitted.

Failure to receive your acknowledgment of this amendment may result in the rejection of your offer.

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